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(54) **BIOMOLECULE DIAGNOSTIC SYSTEMS**

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B01L 3/00 (2006.01)

(52) **U.S. Cl.**
CPC ... ***B01L 3/502738*** (2013.01); *B01L 2200/025* (2013.01); *B01L 2200/026* (2013.01); *B01L 2300/0645* (2013.01); *B01L 2400/0633* (2013.01)

(58) **Field of Classification Search**
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See application file for complete search history.

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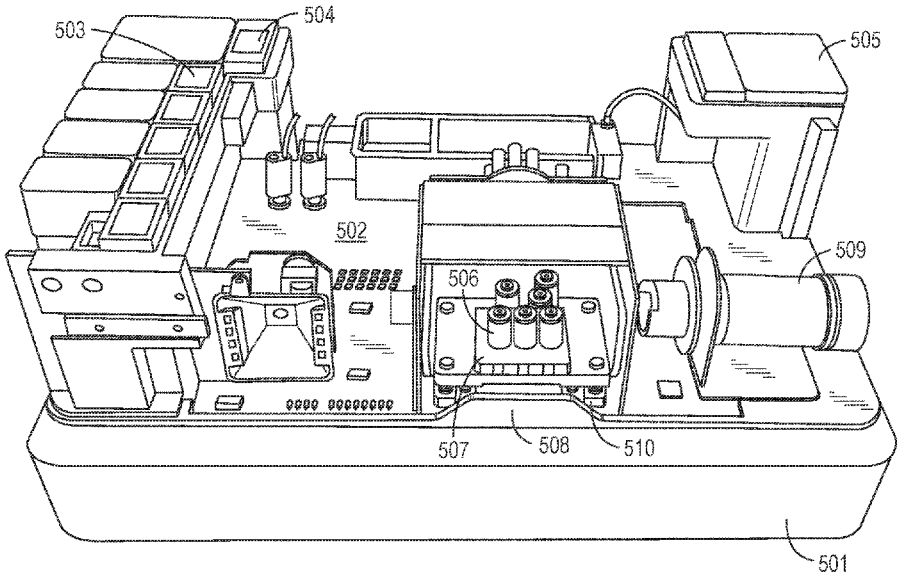
(57) **ABSTRACT**

Diagnostic systems for sensing biological molecules are disclosed. The diagnostic systems include a fluid control delivery and control system that can be coupled to a diagnostic cartridge that includes a microfluidic device and integrated sensing electronics. The diagnostic systems can be used to sequence biological molecules.

15 Claims, 6 Drawing Sheets



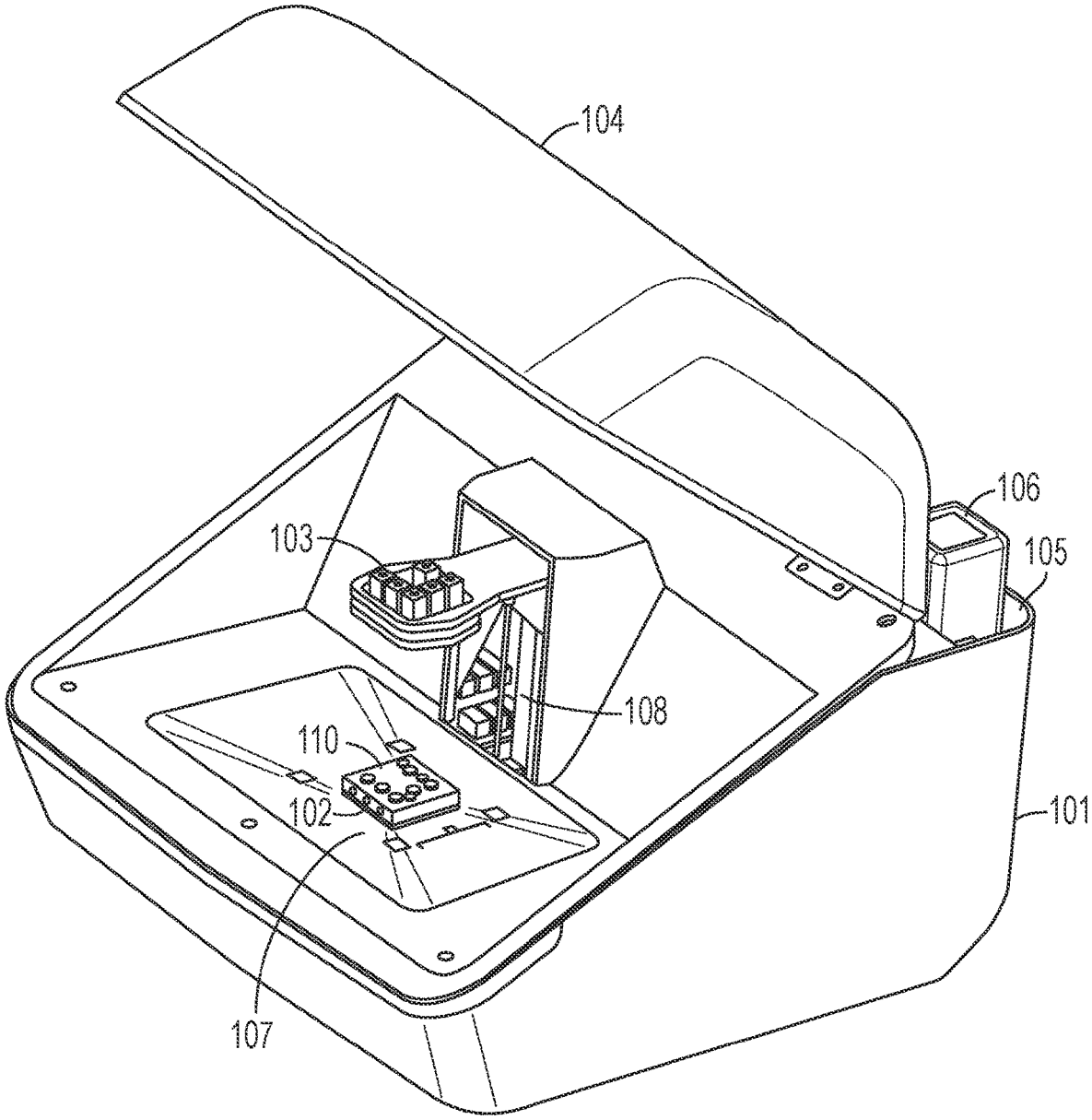


FIG. 1A

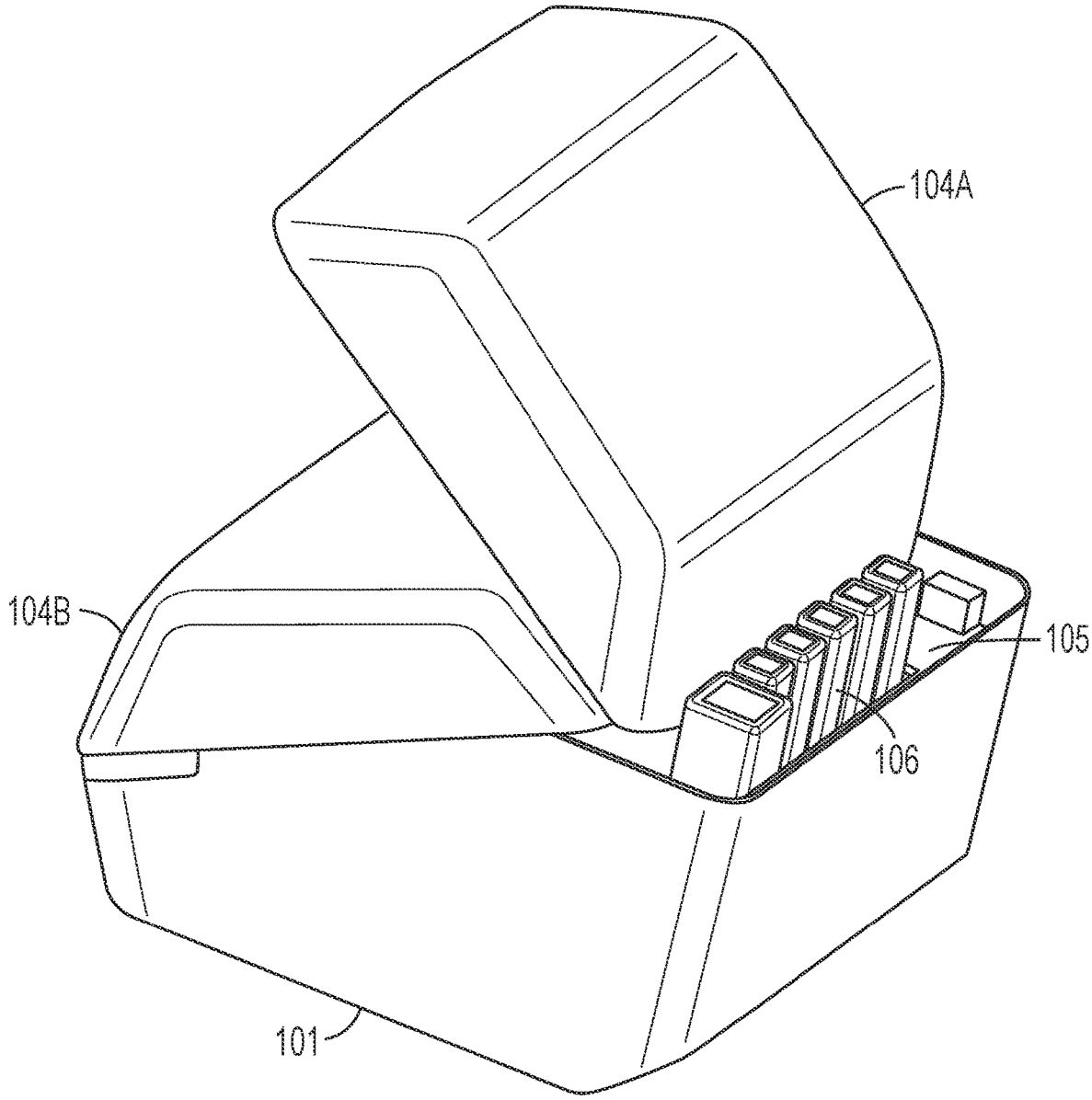


FIG. 1B

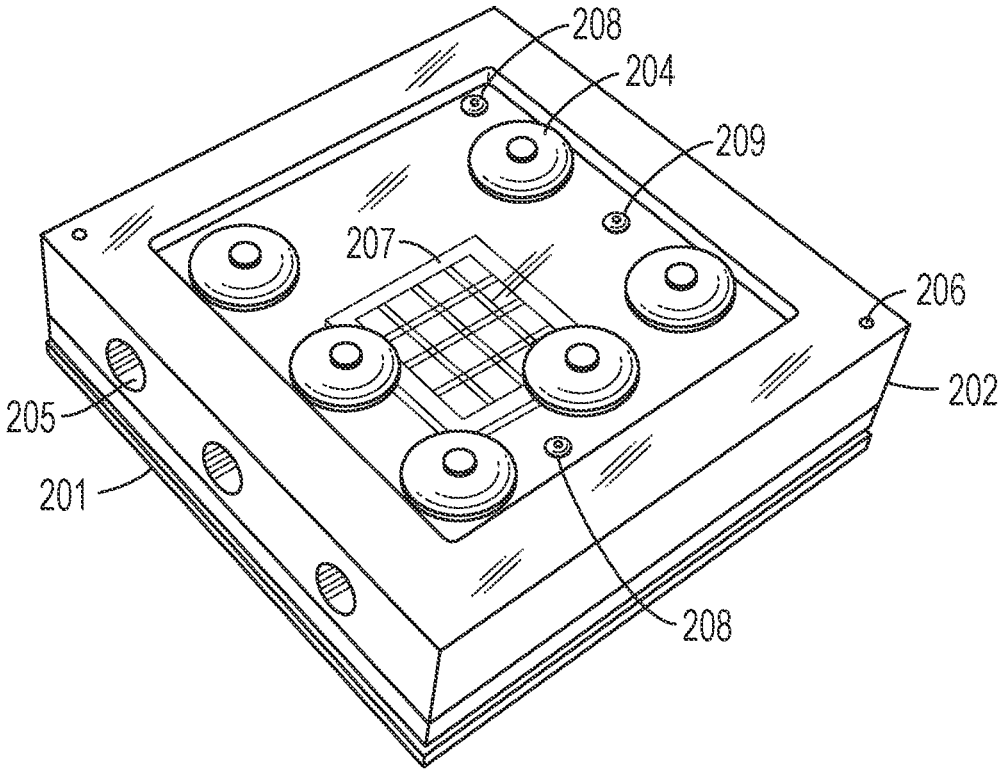


FIG. 2

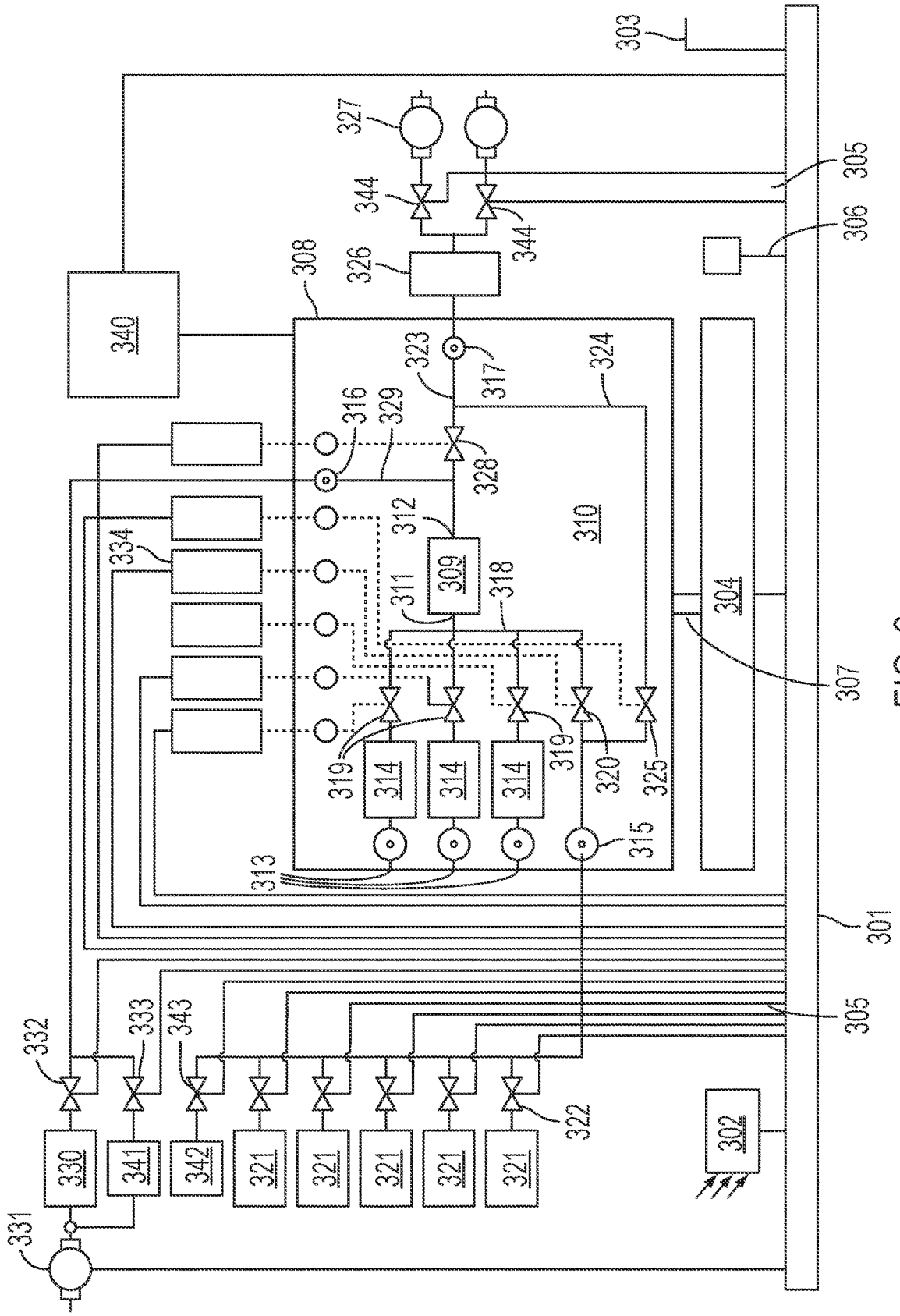

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FIG. 3

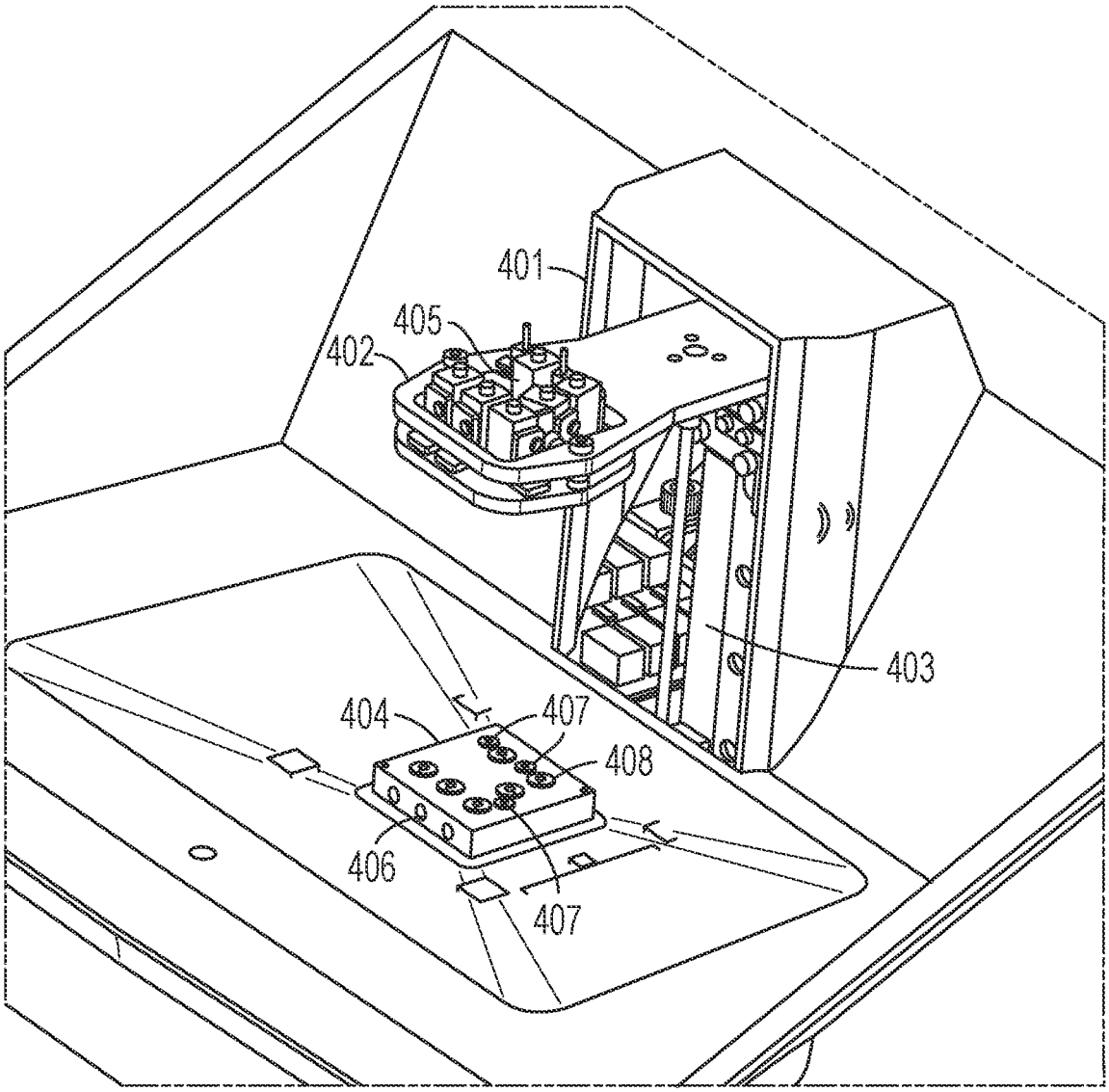

FIG. 4

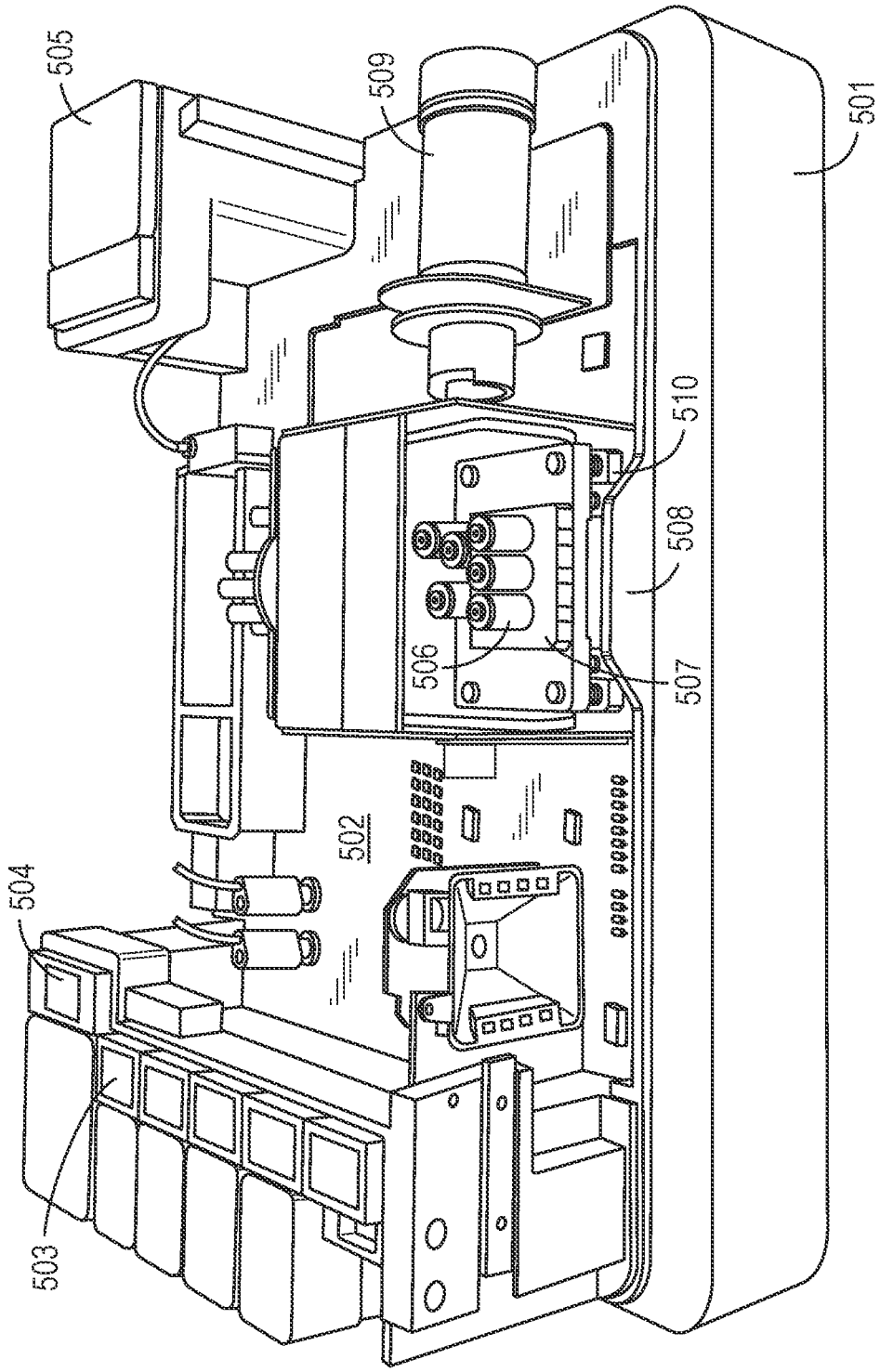

FIG. 5

BIOMOLECULE DIAGNOSTIC SYSTEMS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/867,681, filed on Jun. 27, 2019, which is incorporated by reference in its entirety.

FIELD

The present disclosure relates to diagnostic systems for sensing biological molecules. The diagnostic systems include a fluid control delivery and control system that can be coupled to a diagnostic cartridge that includes a microfluidic device with integrated sensing electronics. The diagnostic systems can be used to sequence biological molecules.

BACKGROUND

Accurate biosequencing can be an expensive and time-consuming process. Improved apparatus that provide accurate and cost-effective sequence information within a reasonable time are desired.

SUMMARY

According to the present invention, diagnostic systems comprise an interconnection substrate; a diagnostic cartridge socket electrically connected to the interconnection substrate; and a fluid management apparatus mounted on a translation stage, wherein the translation stage is configured to fluidly couple the fluid management apparatus to a diagnostic cartridge mounted in the diagnostic cartridge socket.

According to the present invention diagnostic cartridges comprise a cartridge interconnection substrate; a biosensing device interconnected to the cartridge interconnection substrate; and a microfluidics component bonded to the cartridge interconnection substrate and fluidly coupled to the biosensing device.

BRIEF DESCRIPTION OF THE DRAWINGS

Those skilled in the art will understand that the drawings described herein are for illustration purposes only. The drawings are not intended to limit the scope of the present disclosure.

FIGS. **1**A and **1**B show perspective views of an example of a diagnostic system according to the present disclosure.

FIG. **2** shows a perspective view of an example of a diagnostic cartridge according to the present disclosure.

FIG. **3** shows a schematic diagram of an example of a fluid control system according to the present disclosure.

FIG. **4** shows a perspective view of an example of a fluid management apparatus mounted in vertical alignment with a disposable diagnostic cartridge according to the present disclosure.

FIG. **5** shows a perspective view of another example of a diagnostic system according to the present disclosure.

DETAILED DESCRIPTION

For purposes of the following description, it is to be understood that embodiments provided by the present disclosure may assume various alternative variations and step sequences, except where expressly specified to the contrary. Moreover, other than in the examples, or where otherwise indicated, all numbers expressing, for example, quantities of ingredients used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard variation found in their respective testing measurements.

Also, it should be understood that any numerical range recited herein is intended to include all sub-ranges encompassed therein. For example, a range of "1 to 10" is intended to include all sub-ranges between (and including) the recited minimum value of about 1 and the recited maximum value of about 10, that is, having a minimum value equal to or greater than about 1 and a maximum value of equal to or less than about 10. Also, in this application, the use of "or" means "and/or" unless specifically stated otherwise, even though "and/or" may be explicitly used in certain instances.

Diagnostic systems provided by the present disclosure can be used to sense biological molecules. The diagnostic systems include electronics, a socket for electrically interconnecting a diagnostic cartridge, a reagent delivery and reagent control system, and other components. The components can be retained within a housing. The diagnostic systems can be used with a diagnostic cartridge having integrated electronics and microfluidic components and can be provided with simple fluid interfaces and valves for controlling the flow of reagents through the microfluidic component and a biosensing device.

Diagnostic systems provided by the present disclosure provide the ability to sequence biological samples on a massively parallel scale thereby facilitating the ability to provide accurate and reproducible results in a timely manner. The diagnostic cartridge used to sense biological molecules integrates the sensing electronics and microfluidics in a simple physical format and is intended to be disposable. The diagnostic system provides a simple electronic socket interface to control and processing electronics and that can easily be coupled to reagents and flow control components.

Solid views of an example of a diagnostic system provided by the present disclosure are shown in FIGS. **1**A and **1**B. The dimensions of the system can be, for example, less than 12×12×12 in^3 (31×31×31 cm^3). As shown in FIG. **1**A, the diagnostic system includes a housing **101**, a cartridge interface **102**, shown with an interconnected diagnostic cartridge **110**, a fluid management apparatus **103** including fluid delivery and control interface unit **109**, a hinged cover **104**, and a shelf **105** for holding multiple reagent containers **106**. The housing **101** retains, for example, electronics, thermal control elements, a cartridge socket, a fluid management assembly, I/O interfaces, and other elements, which can be mounted on an interconnection substrate.

The base **107** includes a receptacle for retaining and interconnecting a diagnostic cartridge **110** to an interconnection substrate (not shown) retained within the base **107**. A vertical translation stage **108** is mounted toward the back

of the diagnostic system and is used to control, in this example, the vertical position of the fluid delivery and control interface unit **109**. The translation stage **108** is configured to couple the fluid delivery and control interface unit **109** to the diagnostic cartridge **110**. Reagent containers **106** and waste containers (not shown) can be mounted in receptacles located toward the back of the diagnostic system and can be fluidly coupled to the fluid management apparatus **103**.

FIG. **1**B shows a rear view of the diagnostic system highlighting the shelf **105** with multiple reagent containers **106** and with the cover in the open **104**A and closed **104**B configurations

The housing can be made from any suitable material such as a metal, thermoplastic, thermoset, or composite. The hinged cover provides easy access to the diagnostic cartridge socket for inserting and removing a diagnostic cartridge from the socket. The location of the reagent containers external to the covered area facilitates the ability of a user to replace the containers as necessary during operation of the diagnostic system and/or between use of diagnostic cartridges.

Another example of a diagnostic system provided by the present disclosure is shown in FIG. **5**. The diagnostic system shown in FIG. **5** includes a base **501**, a system interconnection substrate **502** which is mounted various control and signal processing electronics, and agnostic cartridge socket **510** mounted on an electrically interconnected to the system interconnection substrate **502**. Fluid management apparatus **507** is shown fluidly coupled to the diagnostic cartridge (hidden), which includes actuators **506** which are fluidly coupled through tubing (not shown) and to reagents **503** and **504** and to waste reservoir **505**. Translator **509** is configured to engage and disengage the fluid management system with the diagnostic cartridge.

Highly integrated sequencing devices can be provided in the form of a disposable diagnostic cartridge that combines a microfluidics component and a biosensing device in a single, integrated package having an area, for example, less than 10 mm^2. The microfluidics component provides an interface between external fluid sources such as reagents and test samples and the biosensing device. The biosensing device is electrically interconnected to control and measurement circuitry integrated into the diagnostic cartridge. As an integrated package, the cartridge provides separable fluidics and electronics interfaces.

A view of an example of a diagnostic cartridge provided by the present disclosure is shown in FIG. **2**. The diagnostic cartridge includes biosensing electronics mounted on an interconnection substrate **201**. A microfluidic component **202** is secured to the interconnection substrate by means of an adhesive. The microfluidics component **202** includes multiple microfluidics layers including, for example, sample reservoirs, fluid routing channels and biosensing cells. A biosensing device **203** is fluidly coupled to microfluidic component **202** and electrically interconnected to the biosensing device interconnection substrate **201**. Flow of reagent and test samples within the microfluidic component **202** and the biosensing device **203** can be controlled by microvalves **204** accessible on the exterior surface of the microfluidic component **202**. Microfluidic component **202** can also include inlet ports **208** and an outlet port **209**. The diagnostic cartridge shown in FIG. **2** includes six (6) microvalves **204**. For example, three (3) microvalves can be used to control the introduction of test sample into the microfluidic component **202** and biosensing device **203**, one (1) microvalve can be used to control the introduction of reagents into the microfluidic component **202** and biosensing device **203**, and two (2) microvalves can be used to control the flow of test sample and/or reagents within and from the microfluidic component **202** and the biosensing device **203**. The microvalves can be normally closed and/or normally open. Suitable microvalves include, for example, membrane-type microvalves and plug-type microvalves that can be controlled by a force applied by an external element such as a solenoid.

The diagnostic cartridge shown in FIG. **2** also includes three (3) side ports **205** that can be used to introduce test sample into respective sample reservoirs within the microfluidic component **202**. The diagnostic cartridge shown in FIG. **2** also includes holes **206** for alignment pins for aligning the diagnostic cartridge to a pad grid array on the underside of the electronics interface with a cartridge socket.

A biosensing device interconnection substrate can be any suitable material such as, for example, a printed circuit board material. A biosensing device interconnection substrate provides an electrical interface between the biosensing device and external electronics. An array of contact pads on the underside of a biosensing device interconnection substrate is configured to separably interconnect the biosensing device with respective connectors of a diagnostic cartridge socket.

A biosensing device can be mounted on and interconnected to the electronic interface and can be fluidly coupled to the microfluidics component at a biosensing device inlet and a biosensing device outlet. The biosensing device includes an array, for example, of from 1,000 to 10,000,000 biosensing cells. Electrodes within each of the biosensing cells are independently accessible through integrated electronics such as CMOS circuitry integrated into the biosensing device interconnection substrate. Biosensing cells include printed a working electrode. The microfluidic component includes a printed counter electrode that is electrically coupled to the working electrodes through fluid within the biosensing device. Each of the biosensing cells is fluidly coupled to the biosensing device inlet and the biosensing device outlet. A biosensing device may or may not incorporate microfluidic control mechanisms.

A microfluidic component can comprise multiple fluidic layers and can include channels, integrated channel valves, and sample reservoirs. The integrated valves can be electrically connected to control circuitry on a system interconnection substrate. The microfluidic layers can be made from any suitable material such as, for example, polycarbonate, poly(methyl) methacrylate, cyclic olefin copolymer, polyimide, or silicone. The microfluidic layers can be fabricated using any suitable process such as by injection molding. The microfluidic layers, biosensing device, and cartridge interconnection substrate can be assembled into an integrated assembly using suitable adhesives.

Diagnostic cartridges provided by the present disclosure can be disposable after a single use. The high level of integration, design simplicity, and use of low-cost materials provides for a cost-effective biosensing solution.

A diagnostic system can include, for example, two levels of temperature control A first level of temperature control can include a temperature sensor coupled to a cooling apparatus such as a fan through a control circuit such as a proportion integrated derivative (PID) circuit. The system level temperature control maintains the internal temperature of the system within a range, for example, from 20° C. to 30° C., when the cover is closed, and the system is operating. A diagnostic system can also include a diagnostic cartridge level temperature control. One or more temperature sensors

situated in the vicinity of the biosensing device can be coupled to a temperature controller such as a Peltier device thermally coupled to the diagnostic cartridge in the vicinity of the biosensing device. Diagnostic cartridge level temperature control can be configured to maintain a constant temperature during operation within a range, for example, from 10° C. to 35° C. The temperature can be maintained, for example, within 1° C., within 2° C., within 3° C., within 4° C., or within 5° C. within the range during a biosequencing operation. Diagnostic cartridge level temperature control can be used to change the temperature during operation such as to perform polymerase chain reactions (PCR). During typical PCR cycles of denaturation, annealing and extension are repeated to amplify a target sequence. Temperatures doting each phase can range, for example, from **94** to **98**, from **48** to **72**, and from **68** to **72**. Each step can take from 0.5 min to 3 min and the PCR cycle repeated from 25 to 35 times.

A schematic of an example of a diagnostic system and in particular the microfluidics of a diagnostic system provided by the present disclosure is shown in FIG. **3**. The diagnostic system shown in FIG. **3** includes a system interconnection substrate **301**. Electronics circuitry including buffers, amplifiers, FIFO, microcontroller (not shown), temperature sensors **302**, I/O interfaces **303**, a diagnostic cartridge socket **304**, microfluidics control circuitry **305**, system temperature control circuitry **306**, diagnostic cartridge temperature control circuitry (not shown), and robotic position control circuitry **340**, are mounted to the interconnection substrate **301**. The diagnostic cartridge socket **304** includes electrical interconnects **307** for interconnecting to the cartridge interconnection substrate (not shown) of the diagnostic cartridge **308**. The electrical interconnects **307** can comprise, for example, an array of spring-loaded micro-connectors.

Robotic positioning system **340** can include a sensing element such as an optical system for aligning the diagnostic cartridge **308** with respect to the diagnostic cartridge socket **304** and/or to the fluid management apparatus (not shown) with respect to the diagnostic cartridge **308**.

Diagnostic cartridge **308** includes a biosensing device **309**, which, for example, can include an array of from 1,000 to 10,000,000 biosensing cells. Diagnostic cartridge **308** also includes a microfluidic component **310**. Microfluidic component **310** includes fluid channels, sample reservoirs, microvalves, inlets, and an outlet. Microfluidic component **310** is fluidly coupled to biosensing device **309** through biosensing device inlet **311** and biosensing device outlet **312**.

Microfluidic component **310** includes one or more sample injection ports **313** for injecting test samples, which can be retained in respective sample reservoirs **314**.

Microfluidic component **310** further includes first cartridge inlet **315**, second cartridge inlet **316**, and cartridge outlet **317**.

Biosensing device inlet **311** is fluidly coupled to inlet channel **318**. Inlet channel **318** is fluidly coupled to sample reservoirs **314** through sample control valves **319**. Sample control microvalves **319** can be activated external to the diagnostic cartridge. Sample control microvalves **319** can be mechanically activated microvalves, such as solenoid-activated microvalves. Referring to FIG. **2**, examples of solenoid-activated microvalves **204** are shown on the upper exterior surface of the microfluidic component **202** of the diagnostic cartridge.

Inlet channel **318** is also fluidly coupled to first cartridge inlet **315** through first cartridge inlet control valve **320**.

First cartridge inlet port **315** can be fluidly coupled to one or more reagent sources **321**. Each of the one or more reagent sources **321** is controllably fluidly coupled to first cartridge inlet port **315** through respective reagent control valves **322**. Reagent sources **321** can be coupled to inlet port **315** using suitable small-diameter tubing. Reagent control valves can be selectively coupled to the cartridge inlet port **315** to provide single reagents or a desired combination of reagents. Reagents can be coupled to control valves and to first cartridge inlet **315** using tubing.

First cartridge inlet port **315** is also coupled to gas source and filter **342** through valve **343**. Gas source **342** can be any suitable gas such as air or argon. Gas source **342** can be used to purge the microfluidics and biosensing device.

Inlet channel **315** can also be fluidly coupled to outlet channel **323** through bypass channel **324** and bypass microvalve **325**.

Biosensing device outlet **312** is fluidly coupled to cartridge outlet port **317** through biosensing device outlet channel **323** and outlet control microvalve **328**. Cartridge outlet port **317** can be fluidly coupled to external waste container **326** and to one or more vacuum pumps **327** controlled by respective vacuum control valves **344**. Biosensing device outlet channel **323** can also be fluidly coupled to second cartridge inlet port **316** through second inlet channel **329**. Second cartridge inlet port **316** can be fluidly coupled to reagent source **330** and to pressure source **331** through control valve **332** and pressure source control valve **333**. Valve **332** and valve **333** are coupled to pressure source **331** through filter **341** to provide a positive pressure at the second inlet port **316**.

Microfluidic component **310** further includes reagent bypass channel **324** fluidly coupling first inlet channel **318** to outlet channel **323** through bypass control microvalve **325**. Bypass channel **324** is coupled to the inlet channel **318** between first cartridge inlet port **315** and first inlet channel control valve **320**, and to the outlet channel **323** between outlet control microvalve **328** and cartridge outlet port **317**.

The one or more sample inlet ports **313** can be disposed on the top or on the side of the microfluidic component **310** of the diagnostic cartridge **308**. Locating the sample inlet ports **313** on the side of the diagnostic cartridge facilitates the ability to inject sample material into the diagnostic cartridge when the diagnostic cartridge is engaged by the fluid management apparatus and interconnected to the cartridge socket.

First cartridge inlet port **315**, cartridge outlet port **317**, sample channel control microvalves **319**, first inlet channel control microvalve **320**, bypass channel control microvalve **325**, and outlet channel control microvalve **328**, and second cartridge inlet port **316** can be disposed on the top surface of the microfluidic component **310**. This placement facilitates the ability of a fluid management apparatus to press onto the top of the diagnostic cartridge and engage with the fluid channels and the microvalves.

The fluid management apparatus can include mechanical actuators **334** for microvalves **319**, **320**, **325**, and **328**, and also fluid couplings for first cartridge inlet port **315**, second cartridge inlet port **316**, and cartridge outlet port **317**.

An example of a fluid management apparatus provided by the present disclosure is shown in FIG. **4**.

Fluid management apparatus **401** includes a platform **402** mounted on a translation stage **403** that lowers the platform to engage the diagnostic cartridge **404** and raises the platform **402** to disengage the components mounted on the platform **402** from a diagnostic cartridge **404**.

In FIG. **4** the platform **402** is shown is being mounted above the diagnostic cartridge **404** and the translation stage **403** operates vertically. However, the diagnostic cartridge can be mounted vertically, and the translation stage can move the platform horizontally to engage with the diagnostic cartridge. Furthermore, although FIG. **4** shows a single diagnostic cartridge and a single fluid management apparatus, a diagnostic system provided by the present disclosure can include more than one diagnostic cartridge and/or more than one fluid management apparatus. For example, a diagnostic system can include more than one diagnostic cartridge and a single fluid management apparatus can move to sequentially engage each diagnostic cartridge. In this configuration, the translation stage can include the ability to translate horizontally as well as vertically. As another example, a diagnostic system can include multiple diagnostic cartridges with each diagnostic cartridge being associated with a separate fluid management apparatus.

Fluid management apparatus **401** can include actuators **405** mounted on platform **402** for controllably actuating respective microvalves **406** on diagnostic cartridge **404**.

Platform **402** can include a self-leveling mount such that a lower element **409** is spring mounted on an upper rigid element. When lowered onto a diagnostic cartridge the lower element **409** engages and can tilt to provide an even pressure to the upper surface of the diagnostic cartridge.

Translation stage **403** can be controlled, for example, using a stepper motor.

Couplings to the first cartridge inlet port, the second cartridge inlet port and the cartridge outlet port can also be integrated into the platform **402** such that the ports are fluidly connected when the fluid management apparatus **401** engages the diagnostic cartridge **404**.

Waste container and vacuum valves can be integrated into the fluid management system or can be external to the fluid management apparatus.

Pressure sources and vacuum sources can be external to the fluid management system and coupled to the fluid management system using appropriate elements.

Injection ports can be used to introduce, for example, biological samples, markers, and membranes.

Microvalves can include, for example, silicone plugs and membrane valves.

Reagents can include, for example, buffers, lipids, macromolecules such as nanopores and/or enzymes, nucleotides, tagged nucleotides, and combinations of any of the foregoing. Reagents can be used to form a nanopore in individual biosensing cells of the biosensing device. For example, a first reagent can comprise a buffer, a second reagent can comprise a buffer and a lipid, a third reagent can comprise an isopropyl alcohol, a fourth reagent can comprise a nanopore, and a fifth reagent can comprise distilled water. Reagents can be used, for example, to prepare the biosensing device, assemble lipid bilayers, introduce nanopores, process biological samples, adjust pH, and clean the system. As an example, the reagents can be sequentially introduced into the biosensing device through the microfluidics channels of the diagnostic cartridge.

Reagents can be purged from the channels and tubing by flowing reagent through bypass channel **324** through valve **325** to waste container **326**.

Pressure can be applied to the microfluidic component using any suitable pump (see element **331** in FIG. **3**). For example, the pressure source can be a peristaltic pump. A pressure source can provide a pressure, for example, from 5 psi to 10 psi.

Pressure can be applied to the microfluidic component using any suitable gas. For example, a gas can be air, nitrogen, or an inert gas such as argon. A filter can be disposed between the pressure source and the gas control valve to prevent gases, oils, and other contaminates from entering the gas control valve and diagnostic cartridge.

A vacuum pump can comprise any suitable vacuum pump such as, for example, a peristaltic pump. FIG. **3** shows two vacuum pumps, although a single pump can be used. It is desirable that a wide range of flow rates be used such as from 0.01 μL/sec to 500 μL/sec, which may be provided by using one or more pumps. To provide for fine control of the flow rate multiple pumps can be used with each pump capable of controlling fluid flow over a portion of the range.

The pressure sources and the vacuum sources can be selectively controlled so that a push/pull action can be applied to the microfluidics channel and to the biosensing device. For example, referring to FIG. **3**, outlet valve **328** and pressure control valve **333** can be alternately opened and closed while other valves are closed to generate positive and negative pressures within the biosensing device and biosensing cells to thereby agitate the fluid within the biosensing cells. This reciprocal motion can disrupt laminar flow and boundary layers.

Reagents may be driven to the diagnostic cartridge by a variety of methods including, for example, application of pressure, application of vacuum, and or by gravity feed. The reagent or combination of reagents entering the diagnostic cartridge can be selectively controlled.

Sequences of polynucleotides contained in a biological sample can be analyzed using the diagnostic system provided by the present disclosure.

Diagnostic cartridges provided by the present disclosure are intended to be disposable following a single use.

One or more biological samples can be injected into respective sample injection ports and retained within respective sample reservoirs. Samples can be loaded while the diagnostic cartridge is mounted in the cartridge socket and engaged with the fluid management apparatus or can be loaded before being mounted in the diagnostic system. After one or more biological samples are delivered into the one or more sample reservoirs, the loaded diagnostic cartridge can be mounted into an electronic socket mounted within the receptacle of the diagnostic system. The same or different biological sample can be delivered to each of the sample reservoirs. A biological sample can comprise, for example, a biological fluid, a polynucleotide, or a protein.

The diagnostic cartridge can be positioned on the diagnostic cartridge socket. The cartridge can be aligned with the socket interconnects such as an array of spring-loaded interconnects by mechanical means such as using alignment pins or by optical means. When aligned, contact pads on the bottom of the diagnostic cartridge rest on respective spring-loaded micro-connectors. The alignment of the socket interconnects, the electrical contact pads on the lower surface of the diagnostic cartridge, the microvalves and ports on the upper surface of the diagnostic cartridge, and the fluid management apparatus can be done manually or robotically.

Mounting the diagnostic cartridge into the electronic socket electrically interconnects the diagnostic cartridge to the electronic interconnection substrate and to the electronics control and I/O circuitry. When mounted in the electronic socket, the fluid control valves on the top surface of the cartridge are positioned such that the fluid control valves are in-line with the valve control mechanism of the fluid management apparatus.

Following initialization, fluid management system can be lowered onto the diagnostic cartridge to engage the microvalves and the cartridge inlet port and the cartridge outlet port on the top surface of the diagnostic cartridge.

After the elements are aligned, the fluid management system can be further lowered onto the diagnostic cartridge to press the cartridge onto the spring-loaded micro-connectors.

The fluid management system is mounted on a self-leveling mount such that pressure is applied evenly to the diagnostic cartridge as the lower spring-loaded element is lowered onto the upper surface of the diagnostic cartridge. Mechanical microvalve activators such as solenoids engage with the septum of the microvalves, and couplings fluidly connect to the inlet and outlet ports.

At this point the diagnostic cartridge can be used for processing and biosensing a biological sample.

During disengagement, the diagnostic cartridge is held against the socket to allow the solenoids to disengage from the microvalves, after which the entire fluid management system can be raised.

Following retraction of the fluid management system, the diagnostic cartridge can be removed, and a new diagnostic cartridge can be inserted into the socket.

ASPECTS OF THE INVENTION

The invention is further defined by the following aspects.

Aspect 1. A diagnostic system, comprising: an interconnection substrate; a diagnostic cartridge socket electrically connected to the interconnection substrate; and a fluid management apparatus mounted on a translation stage, wherein the translation stage is configured to fluidly couple the fluid management apparatus to a diagnostic cartridge mounted in the diagnostic cartridge socket.

Aspect 2. The diagnostic system of aspect 1, wherein the interconnection substrate comprises a printed circuit board.

Aspect 3. The diagnostic system of any one of aspects 1 to 2, wherein the diagnostic cartridge socket comprises a temperature control element operationally coupled to a cartridge temperature sensor.

Aspect 4. The diagnostic system of aspect 3, wherein the temperature control element comprises a Peltier device.

Aspect 5. The diagnostic system of any one of aspects 1 to 4, wherein the diagnostic cartridge socket comprises an array of spring-loaded interconnects.

Aspect 6. The diagnostic system of any one of aspects 1 to 5, wherein the diagnostic cartridge socket comprises a diagnostic cartridge alignment mechanism.

Aspect 7. The diagnostic system of any one of aspects 1 to 6, wherein the fluid management apparatus comprises one or more microvalve actuators.

Aspect 8. The diagnostic system of aspect 7, wherein the one or more microvalve actuators is configured to operationally couple to one or more respective diagnostic cartridge microvalves.

Aspect 9. The diagnostic system of any one of aspects 7 to 8, wherein the one or more microvalve actuators comprise solenoids.

Aspect 10. The diagnostic system of any one of aspects 1 to 9, wherein the fluid management apparatus comprises one or more fluid couplings.

Aspect 11. The diagnostic system of aspect 10, wherein the one or more fluid couplings are configured to fluidly couple to one or more diagnostic cartridge inlet ports or to one or more diagnostic cartridge outlet ports.

Aspect 12. The diagnostic system of any one of aspects 1 to 11, wherein the fluid management apparatus comprises a self-leveling mount.

Aspect 13. The diagnostic system of any one of aspects 1 to 12, further comprising one or more pressure sources and one or more vacuum sources operationally coupled to the fluid management apparatus.

Aspect 14. The diagnostic system of aspect 13, wherein the one or more pressure sources comprise peristaltic pumps.

Aspect 15. The diagnostic system of any one of aspects 13 to 14, wherein the one or more vacuum sources comprise one or more peristaltic pumps.

Aspect 16. The diagnostic system of any one of aspects 1 to 15, wherein the translation stage comprises a stepper motor driven translation stage.

Aspect 17. The diagnostic system of any one of aspects 1 to 6, further comprising an alignment apparatus operationally coupled to the diagnostic cartridge socket, the fluid management apparatus, the translation stage, or a combination thereof configured to be operationally coupled to a diagnostic cartridge.

Aspect 18. The diagnostic system of any one of aspects 1 to 17, further comprising one or more reagent containers fluidly coupled to the fluid management apparatus.

Aspect 19. The diagnostic system of aspect 18, further comprising a valve coupled to each of the one or more reagent containers, wherein the valve is configured to selectively control the reagent or combination of reagents delivered to the fluid management apparatus.

Aspect 20. The diagnostic system of any one of aspects 1 to 19, further comprising a diagnostic cartridge mounted in the diagnostic cartridge socket.

Aspect 21. The diagnostic system of aspect 20, wherein the fluid management system is operationally coupled to the diagnostic cartridge.

Aspect 22. The diagnostic system of any one of aspects 1 to 21, wherein the diagnostic system comprises two or more diagnostic cartridges electrically connected to the interconnection substrate.

Aspect 23. The diagnostic system of any one of aspects 1 to 22, wherein the diagnostic system comprises two or more fluid management apparatus.

Aspect 24. The diagnostic system of any one of aspects 1 to 23, wherein the electronic interconnection substrate is mounted horizontally.

Aspect 25. The diagnostic system of any one of aspects 1 to 23, wherein the electronic interconnection substrate is mounted vertically.

Aspect 26. A diagnostic cartridge, comprising: a cartridge interconnection substrate; a biosensing device interconnected to the cartridge interconnection substrate; and a microfluidics component bonded to the cartridge interconnection substrate and fluidly coupled to the biosensing device.

Aspect 27. The diagnostic cartridge of aspect 26, wherein the cartridge interconnection substrate comprises a printed circuit board.

Aspect 28. The diagnostic cartridge of any one of aspects 26 to 27, wherein the biosensing device comprises from 1,000 to 10,000,000 biosensing cells.

Aspect 29. The diagnostic cartridge of any one of aspects 26 to 28, wherein each of the biosensing cells is configured to be electrically interconnected to a reference electrode, a working electrode, and a counter electrode.

Aspect 30. The diagnostic cartridge of any one of aspects 26 to 29, wherein the biosensing device comprises a biosensing device inlet and a biosensing device outlet.

Aspect 31. The diagnostic cartridge of any one of aspects 26 to 30, wherein the microfluidics component comprises: a first cartridge inlet port fluidly coupled to the biosensing device inlet through an inlet channel; a cartridge outlet port fluidly coupled to the biosensing device outlet through an outlet channel; and a second cartridge inlet port fluidly coupled to the outlet channel and to the biosensing device outlet channel through the second inlet channel.

Aspect 32. The diagnostic cartridge of aspect 31, further comprising: a microvalve disposed between the cartridge inlet port and the biosensing device inlet; and a microvalve disposed between the biosensing device outlet and the cartridge outlet port.

Aspect 33. The diagnostic cartridge of any one of aspects 31 to 32, further comprising: a bypass channel fluidly coupled to the inlet channel and to the outlet channel; and a microvalve disposed within the bypass channel.

Aspect 34. The diagnostic cartridge of any one of aspects 26 to 33, further comprising one or more sample inlet ports fluidly coupled to one or more respective sample reservoirs.

Aspect 35. The diagnostic cartridge of aspect 34, wherein each of the one or more sample inlet ports are disposed on a side of the diagnostic cartridge.

Aspect 36. The diagnostic cartridge of any one of aspects 34 to 35, wherein each of the one or more respective sample reservoirs is fluidly coupled to the biosensing device inlet.

Aspect 37. The diagnostic cartridge of any one of aspects 34 to 36, further comprising one or more sample microvalves disposed between the one or more respective sample reservoirs and the biosensing device inlet.

Aspect 38. The diagnostic cartridge of any one of aspects 26 to 37, further comprising four or more microvalves configured to control fluid flow within the microfluidic component and the biosensing device.

Aspect 39. The diagnostic cartridge of aspect 38, wherein each of the four or more microvalves is disposed on a top surface of the diagnostic cartridge.

Aspect 40. The diagnostic cartridge of any one of aspects 38 to 39, wherein each of the four or more microvalves is mechanically actuated microvalves.

Aspect 41. The diagnostic cartridge of any one of aspects 38 to 39, wherein each of the four or more microvalves is operationally coupled to a mechanical actuator.

Aspect 42. The diagnostic cartridge of any one of aspects 26 to 41, further comprising a temperature sensor disposed proximate to the biosensing device.

Aspect 43. The diagnostic cartridge of any one of aspects 26 to 42, wherein, the first cartridge inlet port is fluidly coupled to one or more reagent containers; the second cartridge inlet port is fluidly coupled to one or more reagent containers and/or to one or more pressure sources; and the cartridge outlet port is fluidly coupled to a waste container and/or to one or more vacuum sources.

It should be noted that there are alternative ways of implementing the embodiments disclosed herein. Accordingly, the present embodiments are to be considered as illustrative and not restrictive. Furthermore, the claims are not to be limited to the details given herein and are entitled their full scope and equivalents thereof.

What is claimed is:

1. A diagnostic system, comprising:

an interconnection substrate;

a diagnostic cartridge socket electrically connected to the interconnection substrate;

a fluid management apparatus mounted on a translation stage, wherein,

the translation stage is configured to fluidly couple the fluid management apparatus to a diagnostic cartridge mounted in the diagnostic cartridge socket; and

the translation stage is configured to fluidly coupled a vacuum source to a diagnostic cartridge mounted in the diagnostic cartridge socket.

2. The diagnostic system of claim **1**, wherein the diagnostic cartridge socket comprises a diagnostic cartridge alignment mechanism.

3. The diagnostic system of claim **1**, wherein the fluid management apparatus comprises one or more microvalve actuators.

4. The diagnostic system of claim **1**, wherein the fluid management apparatus comprises one or more fluid couplings.

5. The diagnostic system of claim **4**, wherein the one or more fluid couplings are configured to fluidly couple to one or more diagnostic cartridge inlet ports or to one or more diagnostic cartridge outlet ports.

6. The diagnostic system of claim **1**, further comprising one or more pressure sources and one or more vacuum sources operationally coupled to the fluid management apparatus.

7. The diagnostic system of claim **1**, further comprising a diagnostic cartridge mounted in the diagnostic cartridge socket.

8. The diagnostic system of claim **7**, wherein the fluid management system is operationally coupled to the diagnostic cartridge.

9. A diagnostic cartridge, comprising:

a cartridge interconnection substrate;

a biosensing device interconnected to the cartridge interconnection substrate, wherein the biosensing device comprises:

a plurality of biosensing cells; and

a biosensing device inlet and a biosensing device outlet; and

a microfluidics component bonded to the cartridge interconnection substrate and fluidly coupled to the biosensing device;

a first cartridge inlet port fluidly coupled to the biosensing device through a cartridge inlet channel;

a cartridge outlet port fluidly configured to be coupled to the biosensing device through a cartridge outlet channel;

a second cartridge inlet port configured to be fluidly coupled to the cartridge outlet channel and to the cartridge inlet channel;

the second cartridge inlet port is configured to be fluidly coupled to one or more pressure sources; and

the cartridge outlet port is configured to be fluidly coupled to one or more vacuum sources.

10. The diagnostic cartridge of claim **9**, wherein each of the biosensing cells is configured to be electrically interconnected to a reference electrode, a working electrode, and a counter electrode.

11. The diagnostic cartridge of claim **9**, further comprising one or more sample inlet ports fluidly coupled to one or more respective sample reservoirs.

12. The diagnostic cartridge of claim **11**, further comprising one or more sample microvalves disposed between the one or more respective sample reservoirs and the biosensing device inlet.

13. The diagnostic cartridge of claim 9, further comprising four or more microvalves configured to control fluid flow within the microfluidic component and the biosensing device.

14. The diagnostic cartridge of claim 9, further comprising a temperature sensor disposed proximate to the biosensing device.

15. The diagnostic cartridge of claim 9, wherein,

the first cartridge inlet port is fluidly coupled to one or more reagent containers;

the second cartridge inlet port is fluidly coupled to one or more reagent containers and/or to one or more pressure sources; and

the cartridge outlet port is fluidly coupled to a waste container and to one or more vacuum sources.

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